REMARKS

The foregoing amendments and the following remarks are submitted for entry and consideration in connection with the Request for Continued Examination and in response to the communication dated April 19, 2005 and the Advisory Action dated August 17, 2005.

Status of the Claims

Claims 14-17 are pending in the application. Claims 14 and 15 have been amended in order to more particularly point out and distinctly claim that which Applicants regard as the invention. Support for the amended claims can be found generally through Applicants' Specification.

The 35 U.S.C. 112, First Paragraph, Rejection

Claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner sets this rejection out as a new matter rejection, asserting that the recitation "and do not give rise to functional gametes" is considered new matter because there is no description in the Specification for a pluripotent embryonic-like stem cell that does not give rise to functional gametes. In conjunction with this rejection, the Examiner rejects claims 14-17 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the Specification as to enable the skilled artisan to make and/or use the invention. Applicants respectfully disagree and submit that the Specification enables the skilled artisan to make and/or use the invention and provides support for and describes a pluripotent embryonic-like stem cell, which is not a totipotent cell and thereby does not give rise to functional gametes. The Specification teaches, including at page 3, lines 29-31, that embryonic stem cells are "totipotent", giving rise to all somatic lineages as well as functional gametes. The pluripotent embryonic-like stem cells of the invention are just that – pluripotent and NOT totipotent. The definition and description of a totipotent cell is set out at page 3 as provided above (and in Applicants prior response) and at page 1, lines 22-25, where it states:

> This process begins with the totipotent zygote and continues throughout the life of the individual. As development proceeds

> from the totipotent zygote, cells proliferate and segregate by lineage-commitment into the pluripotent primary germ layers, ectoderm, mesoderm and endoderm.

Thus, the Specification sets out a distinction between totipotent cells and pluripotent cells from the first page. A totipotent cell can form somatic cells from all three embryonic layers, e.g. ectoderm, mesoderm, and endoderm, as well as forming functional gametes. The Specification defines pluripotent embryonic-line stem cells, including at page 9, lines 5 through 11, as capable of self-regeneration and capable of differentiation to cells of endodermal, ectodermal and mesodermal lineages. Pluripotent cells are not totipotent and they cannot form functional gametes. Nowhere in the Specification does it state or suggest that the pluripotent embryonic-line stem cells of the invention will form gametes. It is only stated that the pluripotent embryonic-line stem cells will form somatic cells from all three embryonic lineages – ectoderm, mesoderm, and endoderm – and are thus pluripotent. In fact, attempts by Applicants and the inventor to identify the formation of gametes from the pluripotent embryonic-line stem cells of this invention have been unsuccessful. Applicants can provide a declaration stating and/or evidencing that the PPELSCs have not been demonstrated to form gametes.

In view of the foregoing remarks, Applicants submit that the Examiner's 112, first paragraph, rejections are obviated and should be withdrawn.

Particularity and Distinctiveness of the Claims

The Examiner has rejected claims 14-17 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter Applicant regards as the invention. The Examiner asserts that the metes and bounds of the term "each and any" is unclear. Applicants point out that the intent of the each and any language is to recite the novel capacity of the pluripotent embryonic-like stem cells of the invention to differentiate to cells which are derived from all of the lineages – ectodermal, and endodermal and mesodermal. Applicants have above amended claims 14 and 15 to delete the rejected language and to clarify the claim. Applicants assert that the language of the claims is clear as presently presented, reciting that the stem cells differentiate to cells derived from all of the three lineages.

In view of the foregoing amendment and remarks, Applicants submit that the Examiner's 112, second paragraph, rejection is obviated and should be withdrawn.

The §102 Rejections

The Examiner has again rejected claims 14-16 under 35 U.S.C. 102(b) as being anticipated by Capecchi et al [Scientific American 270(3): 34-41 (1994)]. Capecchi teaches the inactivation of target genes by homologous recombination and the insertion of a *neo* resistance gene, which serves as a positive selection marker, in mouse ES cells. The Examiner asserts that the claimed cells are not distinguished from those taught by Capecchi. The Examiner remarks that not all totipotent cells give rise to functional gametes, although they can give rise to functional gametes. It is equally possible that ES cells do not give rise to functional gametes, the Examiner remarks, as evidenced by the need to screen chimeric mice for evidence of germ-line transmission. Applicants respectfully disagree and again assert that Capecchi et al does not anticipate claims 14-16. The pluripotent embryonic-like stem cells of Applicants, as claimed, are not anticipated by the ES cells of Capecchi – they differ as a product, as well as being isolatable from a non-embryonic or postnatal cell (i.e., made by a different process). Applicants agree that ES cells can and often do give rise to gametes, however, the nature and limited efficiency of generating transgenic animals from ES cells results in some animals with gamete transmission and others where ES cells have not populated gametes in the transgenic animal. The important point and distinction factually is that totipotent cells, including ES cells, can give rise to gametes by definition, where the pluripotent embryonic-like stem cells of Applicants cannot. The requirement to screen chimeric mice is as much a function and fact of the overall inefficiency of the process of genetic manipulation and generation of transgenic mice per se, as it is a reflection of the percentage, on a cell by cell basis, of totipotent ES cells which become gametes. In any event, Applicants argue that this is not relevant to the rejection because ES cells are totipotent and can form gametes, while pluripotent embryonic-like stem cells of this invention are pluripotent, not totipotent, and cannot form gametes. This is a distinction and difference in fact. Applicants PPELSCs are not taught or anticipated by the ES cells of the Capecchi et al reference.

The Examiner has maintained the rejection of claims 14-17 under 35 U.S.C. 102(b) as

anticipated by Povey et al [Blood 92(11): 4080-4089 (1998)], which teaches the transfection of hematopoietic stem cells using a retroviral vector. The Examiner asserts that the instant claims fail to be distinguished from the cells taught by Povey, which are hematopoietic stem cells capable of multilineage differentiation and self-renewal, because Applicants claims encompass cells which differentiate to each of the three lineages or combinations of these lineages. Applicants strongly disagree and argue that the transfected hematopoietic stem cells of Povey, capable of differentiation only to hematopoietic cells, which are one type of mesodermal cell, do not anticipate the claimed cells of the instant Application. Applicants point out that the language of claims 14 and 15 has above been amended and clarified. The pluripotent embryonic-like stem cells of the instant Application differentiate to cells derived from all of the endodermal, ectodermal and mesodermal lineages. The PPELSCs are importantly distinct from hematopoietic stem cells, such as Povey's, which differentiate to cells at only the hematopoietic lineage (a mesodermal origin lineage). A cell which can ONLY differentiate to a single (mesodermal for instance) lineage cannot and does not anticipate a cell which can differentiate to all three (ecto, endo and mesodermal) lineages. The hematopoietic stem cells of Povey have a more limited differentiative capacity along a single lineage, and do not teach or anticipate the PPELSCs stem cells of Applicants.

The Examiner again rejects claims 14-17 under 35 U.S.C. 102(b) over Verma et al [Gene Therapy 5:692-699 (1998)], which describes the transfection of hematopoietic progenitor cells (hematopoietic stem cells (HSCs)) using a CMV-CAT reporter plasmid. The Examiner argues that Verma teaches transfection of HSCs, which are capable of differentiation to at least one of the lineages (mesoderm) required by the claims, and therefore anticipates the claims. Applicants disagree and point out that claims 14 and 15 have been above amended to clarify the language setting out the distinction of the stem cells of this invention. The hematopoietic progenitor cells of Verma are able to differentiate into cells of only the hematopoietic lineage and do not anticipate the isolated pluripotent embryonic-like stem cells of the instant Application. The pluripotent embryonic-like stem cells of the instant Application differentiate to cells derived from all of the endodermal, ectodermal and mesodermal lineages. The PPELSCs are importantly distinct from stem cells, such as Verma's, which differentiate along only one or at most two of

the lineages. Again, the hematopoietic stem cells of Verma have a more limited differentiative capacity and do not in fact teach or anticipate the pluripotent embryonic-like stem cells of Applicants.

Claims 14-16 are further rejected under 35 U.S.C. 102(b) as being anticipated by Piedrahita et al [Biol of Reprod 58:1321-1329 (1998)], which teaches the generation of transgenic porcine chimeras using primordial germ cells (PGCs)-derived colonies. The Examiner asserts that Piedrahita anticipates the claimed invention because the PGCs they teach are capable of differentiation into the three germ layers. Applicants respectfully submit that Piedrahita et al does not anticipate or teach the pluripotent embryonic-like stem cells of the instant Application. Piedrahita teaches that the chimeric cells contributed to the germ line. At page 1321 in the Introduction, second column, Piedrahita states:

> Recently, murine cell lines derived from primordial germ cells were found to behave similarly to ES cells and to be capable of contributing to the germ line [16]. These cells, referred to as embryonic germ (EG) cells or primordial germ cell (PGC)-derived cells [16,17], are similar to ES cells with respect to markers of the undifferentiated state and their ability to colonize the germ line following injection into a host blastocyst; however, they differ in the extent of methylation of specific genes [16].

Contribution to the germ line necessitates the ability to form gametes, such that the cells can contribute to progeny and transmit a genetic marker to subsequent generations through eggs and/or sperm. Thus, the PGCs of Piedrahita, similar to ES cells, are totipotent, forming cells from all three germ layers – ectoderm, endoderm, and mesoderm – and forming gametes to contribute to the germ line. The pluripotent embryonic-like stem cells of the instant Application differentiate to cells derived from all of the endodermal, ectodermal and mesodermal lineages, but cannot form gametes and thus do not contribute to the germ line; PPELSCs are not totipotent. The cells of the Piedrahita et al reference do not teach or anticipate the PPELSC stem cells identified and claimed by Applicants.

In view of the foregoing amendments and remarks, Applicants submit that the Examiner's

102 rejections are obviated and should be withdrawn.

The §103 Rejections

The Examiner maintains the prior rejection of claims 14-17 under 35 U.S.C. 103(a) over Pittenger et al [Science 284:143-147 (1999)] in view of Sambrook et al [Molecular Cloning, Book 3, 1989]. Pittenger teaches human mesenchmyal stem cells which are found to differentiate into multiple mesenchmyal (i.e., mesoderm derived) lineages *in vitro*. Sambrook teaches methods of transfecting mammalian cells with any gene of interest. The Examiner asserts that the claims are written in the alternative, and do not require differentiation into all three lineages, endodermal, ectodermal and mesodermal. Applicants respectfully disagree and submit that the cells as claimed by Applicants are not obvious over Pittenger in view of Sambrook. Applicants have above amended the language of claims 14 and 15 in order to clarify the intent of the claims. The human mesenchmyal stem cells of Pittenger are capable of differentiating into cells of only the mesenchmyal lineage. The pluripotent embryonic-like stem cells of this Application, as claimed, differentiate to cells derived from all of the endodermal, ectodermal and mesodermal lineages. The PPELSCs are importantly distinct from stem cells, such as Pittenger's, which can differentiate to only one or two of the lineages. This differentiation capacity is not in the alternative and is not anticipated or made obvious by stem cells capable of differentiating into only a single or even two lineage type(s). The cells of Pittenger, mesenchmyal stem cells, have a limited differentiative capacity to only mesenchmyal lineage cells; the Pittenger cells cannot form cells of the ectodermal or of the endodermal lineage. Pittenger does not, when combined with the teachings of Sambrook, render the pluripotent embryonic-like stem cells claimed by Applicants obvious.

Claims 14-17 are further rejected under 35 U.S.C. 103(a) over Shamblott [PNAS 95:13726-13731 (1998)] in view of Sambrook et al [Molecular Cloning, Book 3, 1989]. Shamblott et al teach the generation of human pluripotent stem cells from gonadal ridges and mesenteries containing primordial germ cells (PGCs) and teach that embryoid bodies collected from these cultures revealed a wide variety of differentiated cell types, including derivatives of

all three embryonic germ layers. Sambrook teach methods of transfecting mammalian cells with any gene of interest. The Examiner remarks that the instant claims do not provide any requisite characteristics of the claimed stem cells such that they would be distinguished from the cells taught by Shamblott. Applicants respectfully disagree and assert that the cells identified and claimed by Applicants are not rendered obvious by the combination of the Shamblott and Sambrook references. The pluripotent embryonic stem cells are distinct from embryonic stem cells and primordial germ cells, particularly in that they are pluripotent and are not totipotent – they do not give rise to functional gametes. As noted above with regard to the Piedrahita et al reference, primordial germ cells were found to behave similarly to ES cells and to be capable of contributing to the germ line, thus being "totipotent" and forming gametes. This is noted in the Shamblott reference, where at page 13726, in the first paragraph of the introduction, it states:

> Embryonic stem (ES) cells are derived from the inner mass of preimplantation embryos (1,2), and embryonic germ (EG) cells are derived from primordial germ cells (PGCs) (3,4). Both ES and EG cells are pluripotent and demonstrate germ-line transmission in experimentally produced chimeras (5,6).

The PGCs of Shamblott, similar to ES cells are totipotent, forming cells from all three germ layers – ectoderm, endoderm, and mesoderm – and also forming gametes to demonstrate germ-line transmission. The pluripotent embryonic-like stem cells of the instant Application cannot form gametes and thus do not contribute to the germ line. The cells of the Shamblott et al reference do not teach or anticipate the stem cells identified and claimed by Applicants and the combination of Shamblott with the teachings of Sambrook does not render obvious the pluripotent embryonic-like stem cells claimed by Applicants.

The Examiner again rejects claims 14-17 under 25 U.S.C. 103(a) as being unpatentable over Thomson [Reference BR on Applicants' IDS filed 7/3/03, PNAS USA 92:7844-7848 (1995)] taken with Sambrook [Molecular Cloning, Book 3, 1989]. Thomson teaches the isolation of embryonic stem (ES) cells from the rhesus monkey, which differentiated into cells of endoderm, mesoderm and ectoderm. Sambrook teaches methods of transfecting mammalian cells with any gene of interest. Applicants again assert that the claimed pluripotent embryonic-like stem cells are distinct and unobvious from ES cells, which are totipotent cells, and are also

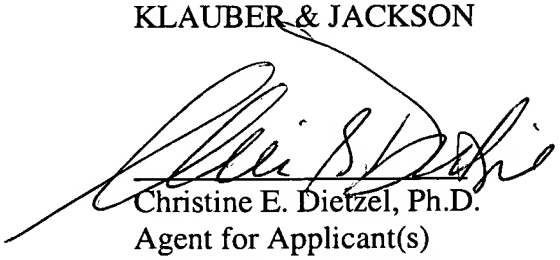
not made obvious by the combination of ES cells taught in Thomson with the transfection of mammalian cells taught by Sambrook. ES cells are totipotent and are capable of giving rise to all somatic lineages (ectodermal, endodermal and mesodermal) as well as functional gametes. The pluripotent embryonic-like stem cells of the present invention are pluripotent and are capable of differentiation to somatic cells of any endodermal, ectodermal, mesodermal lineage, but are not totipotent – they do not give rise to functional gametes. The combination of Thomson and Sambrook does not make obvious the genetically engineered pluripotent embryonic-like stem cells as claimed by Applicants.

In view of the foregoing amendments and remarks, Applicants submit that the Examiner's 103 rejections are obviated and should be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Should the Examiner feel that further issues remain upon a review of this Response, he is invited to call the undersigned at the number listed below to effect their resolution. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,
KLAUBER & JACKSON



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